Radiosurgery for nonfunctioning pituitary adenoma

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Object. Nonfunctioning pituitary adenomas comprise approximately 30% of all pituitary tumors. The purpose of this retrospective study was to evaluate the efficacy and role of gamma knife surgery (GKS) in the treatment of these lesions.

Methods. The authors conducted a review of cases in which GKS was performed at the University of Pittsburgh between 1987 and 2001. Forty-six patients with nonfunctioning pituitary adenomas and with at least 6 months of follow-up data were identified. In 41 of these patients some form of prior treatment such as transsphenoidal resection, craniotomy and resection, or conventional radiation therapy had been conducted. Five patients were deemed ineligible for microsurgery, and GKS served as the primary treatment modality. Endocrinological, ophthalmological, and radiological responses were evaluated. The mean radiation dose to the margin was 16 Gy.

In all patients with microadenomas and 91% of those with macroadenomas tumor control was demonstrated after radiosurgery. Gamma knife surgery had essentially equal efficacy in terms of achieving tumor control in cases of adenomas with cavernous sinus invasion and suprasellar extension. No new endocrinopathies were noted following radiosurgery. In two patients, however, tumor growth and decline in visual function occurred.

Conclusions. Gamma knife surgery is safe and effective in treating nonfunctioning pituitary adenomas. Radiosurgery may serve as a primary treatment modality in some or as a salvage treatment in others. Treatment must be tailored to meet the patient’s symptoms, overall health, and tumor morphometry.

KEY WORDS • gamma knife • pituitary adenoma • null cell • radiosurgery

Pituitary adenomas are common lesions and represent 10 to 20% of all primary brain tumors. The authors of epidemiological studies have demonstrated that nearly 20% of the general population harbor a pituitary adenoma. Pituitary adenomas are broadly classified into two groups. In the first category are those that secrete excess amounts of normal pituitary hormones and, consequently, present with a variety of clinical syndromes depending on the types of hormones secreted. The most common of these is the prolactin-producing adenoma (or prolactinoma), which causes amenorrhea–galactorrhea in women and impotence and infertility in men. Fortunately, prolactinomas can usually be managed medically with dopamine agonist drugs. The second most common functioning pituitary adenoma is the growth hormone–secreting variant in which patients present with acromegaly and, sometimes, gigantism. Adrenocorticotropic hormone–secreting tumors produce Cushing disease or, if bilateral adrenocortical function has been impaired, Nelson syndrome.

The second category of pituitary adenomas is composed of tumors that do not secrete any known biologically active pituitary hormones, and these represent approximately 30% of all pituitary tumors. These so-called nonfunctioning or null-cell pituitary adenomas progressively enlarge in the pituitary fossa and may even extend outside of the confines of the sella turcica. These tumors may cause symptoms related to mass effect in which the optic nerves and chiasm are compressed, and a bitemporal visual field loss characteristically results. Patients harboring large nonfunctioning adenomas can also suffer hypopituitarism secondary to compression of the normal functioning pituitary gland.

For both types of pituitary adenomas, recurrence due to invasion of the tumor into surrounding structures or incomplete resection is quite common. Long-term tumor control rates after microsurgery alone varies from 50 to 80%. Radiotherapy or radiosurgery can be administered postoperatively as prophylaxis to inhibit recurrent growth or, later, when clinical symptoms or radiographic signs indicate recurrence. They may also be performed postoperatively to treat known residual tumor after incomplete resection. The presence of residual tumor is not uncommon in patients harboring adenomas with either a suprasellar component or cavernous sinus involvement.

Abbreviations used in this paper: GK = gamma knife; GKS = GK surgery.
Less often, radiosurgery is chosen as the primary treatment in patients determined ineligible for resection (either transsphenoidal or craniotomy) or those with incidentally found nonfunctioning adenomas.

Much has been written about functioning pituitary adenomas treated with radiosurgery and conventional fractionated radiotherapy. The focus of this research is to define better both the role and the utility of GKS for nonfunctioning pituitary adenomas.

**CLINICAL MATERIAL AND METHODS**

A retrospective review was conducted of cases in which nonfunctioning pituitary adenomas were treated with GKS at the University of Pittsburgh between 1987 and 2001. All procedures were performed using either the model U or model B/C GK units (Elekta Corp., Atlanta, GA). Radiosurgery was performed by either L.D. or D.K. The radiosurgical methodology used to treat pituitary lesions has been detailed elsewhere. A representative dose plan is pictured in Fig. 1. All patients underwent extensive endocrinological evaluation prior to treatment, and no evidence of excess pituitary hormone secretion was noted. Patients with visual dysfunction underwent appropriate ophthalmological evaluation prior to radiosurgery. Only those patients with a minimum of 6 months of follow-up data were included in the present study.

A total of 46 patients met the aforementioned criteria. Analysis of postradiosurgery imaging studies was performed to determine if the volume of each lesion had increased, decreased, or remained the same. Tumor control was defined as either decreased or unchanged tumor volume at follow-up evaluation. Clinical follow-up studies typically included endocrinological and neuroophthalmological evaluations as well as subjective reports from the patients themselves.

The patient population was composed of 28 male and 18 female patients (Table 1). At the time of radiosurgical treatment, the mean age was 55.5 years (range 15–88 years). Forty-one patients had undergone previous treatments including transsphenoidal resection, craniotomy and resection, and conventional radiotherapy (Table 1). Radiosurgery was the initial treatment modality in five patients who had been deemed ineligible for conventional resection because of other comorbidities such as concurrent debilitating cardiopulmonary disease. Thirteen patients presented with microadenomas and 33 patients with macroadenomas. The mean follow-up period was 26.5 months (range 6–102 months). Twenty-nine patients underwent follow up for more than 12 months.

Forty-six patients with nonfunctioning pituitary adenomas underwent radiosurgery at the University of Pittsburgh. A total of 47 radiosurgical procedures were performed. One of these patients harbored a macroadenoma which was treated in two stages. The radiosurgical parameters and dose selection varied depending on the adenoma size, location (for example, proximity to the optic apparatus), and history of radiotherapy. Maximum tumor doses ranged from 20 to 70 Gy (mean center dose 31.9 Gy). The mean marginal dose for all adenomas was 16.0

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*Fig. 1. Representative radiosurgical dose plan. This representative dose plan was used in the treatment of a patient with nonfunctioning pituitary adenoma with cavernous sinus extension. The numbers surrounding the adenoma denote isodose curves.*
Radiosurgery for nonfunctioning pituitary adenoma

TABLE 1
Characteristics of patients with nonfunctioning pituitary adenomas treated with radiosurgery

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>sex</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>28</td>
</tr>
<tr>
<td>female</td>
<td>18</td>
</tr>
<tr>
<td>mean age (yrs)</td>
<td>55.5 (range 15-88)</td>
</tr>
<tr>
<td>mean no. of previous treatments (range)</td>
<td></td>
</tr>
<tr>
<td>transsphenoidal resection</td>
<td>0.80 (0–4)</td>
</tr>
<tr>
<td>craniotomy/resection</td>
<td>0.24 (0–3)</td>
</tr>
<tr>
<td>radiotherapy</td>
<td>0.20 (0–1)</td>
</tr>
<tr>
<td>mean follow-up post-GKS (mos)</td>
<td>26.8 (range 6-102)</td>
</tr>
</tbody>
</table>

Gy, but these doses to the margin ranged between 10 and 34 Gy. The mean dose to the optic apparatus was 7 Gy. Rarely, the dose to the optic apparatus exceeded 8 Gy, occurring in the pre–magnetic resonance imaging era of radiosurgical treatment at the University of Pittsburgh. The mean number of isocenters per adenoma was 5.8 (range 1–20). Overall, in treating these pituitary adenomas, the 8-mm collimator was the most frequently utilized.

In all patients either growth of the adenoma was demonstrated on sequential neuroimaging studies or symptoms (such as headaches) believed to be related to the adenoma were exhibited. An analysis of a subset of the patients with recurrent adenomas has been previously published.25

Statistical analysis was performed with the aid of commercially available software (StatView 4.5.1; Abacus Concepts, Inc., Berkeley, CA). The Student t-test was performed when appropriate, and statistical significance was set as a probability of less than 0.05.

RESULTS

In this group of 46 patients, the pituitary adenomas’ attributes varied. Thirteen were microadenomas, and radiosurgery achieved tumor control in 100%. Thirty-three lesions were macroadenomas and control was achieved in 91%. Of the three patients with macroadenomas, in whom radiosurgery failed to control disease, two underwent repeated transsphenoidal resection after experiencing visual function deterioration, and the third died of complications related to a grand mal seizure 16 months after radiosurgery. In 25 of the tumors, cavernous sinus extension was observed, and a tumor control rate of 92% was achieved. In nine adenomas with suprasellar extension, the control rate was slightly less at 89%. The absolute numbers of those patients in each subgroup in whom GKS succeeded and failed are graphically depicted in Fig. 2.

When grouped together, the tumor volumes decreased or remained unchanged in 43 (93%) of 46 patients treated. Sixteen of these adenomas actually decreased in size after radiosurgery while 27 remained stable. The mean radiation dose to the margin of those adenomas that increased in size was 14 compared with 15.8 Gy in those that either decreased or remained unchanged. There was no statistically significant difference, however, between either the margin or maximum doses in the groups in which radiosurgery succeeded and those in which it failed (p > 0.05, Student t-test).

Patients with nonfunctioning pituitary adenomas presented with symptoms of endocrinological dysfunction, visual disturbances, and headaches (Table 2). In all 30 patients with endocrinological deficiencies signs typically included deficiencies in cortisol, thyroid, and gonadotropin hormones. One patient with endocrinological dysfunction did experience an improvement and was weaned from some of her hormonal supplementation postradiosurgery. No patient suffered new endocrinopathy following radiosurgery. Twenty patients experienced some form of visual disturbance (for example, retinopathy or decreased visual fields) associated with their pituitary adenoma. Of those with visual dysfunction, two patients (10%) improved and 16 (80%) regained stable visual function after radiosurgery. Two patients (10%) suffered visual deterioration in the months following radiosurgery. Both of these patients harbored macroadenomas and ultimately required surgical debulking of their tumors. Of 10 patients with preoperative headaches, two experienced improvement. Following radiosurgery, one patient suffered worsening of chronic headaches. Additionally another patient developed postoperative headaches that ultimately resolved.

DISCUSSION

There are multiple treatment modalities for nonfunctioning pituitary adenomas. Potential treatments include microsurgery via either transsphenoidal- or craniotomy-based approaches, radiotherapy, and radiosurgery. The specific treatment must be tailored to a patient’s symptoms, overall health, and tumor morphometry. Transsphenoidal resection is one of the most popular types of treatments for pituitary adenomas, and it is clearly indicated in cases of apoplexy or when tumor growth rapidly compromises visual function. Even in the best of hands, however,
TABLE 2

<table>
<thead>
<tr>
<th>Presenting Symptom</th>
<th>No. of Cases</th>
<th>No. W/ Improved or Stable Symptoms</th>
<th>No. W/ Worsening Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>endocrinological dysfunction</td>
<td>30</td>
<td>30 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>visual disturbances</td>
<td>20</td>
<td>18 (90)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>headaches</td>
<td>10</td>
<td>8 (80)</td>
<td>2 (20)</td>
</tr>
</tbody>
</table>

microsurgery alone provides long-term control rates in the range only 50 to 80% of cases.\textsuperscript{2,10,11,18} Residual or recurrent tumor originating in areas traditionally difficult to resect via a transsphenoidal approach (for example, suprasellar or cavernous sinus extensions), may proliferate, and symptoms associated with the adenoma may return.\textsuperscript{6}

The use of radiological and radiation-based techniques in the treatment of pituitary lesions is not a new phenomenon. With the advent of roentgenograms in 1896, it was evident that the sella turcica could be visualized on x-ray films and that enlargement of the osseous structure was frequently associated with neuroendocrinological disease. Pituitary tumors were some of the first brain lesions to be treated using conventional radiotherapy.\textsuperscript{3} Initial approaches involved horizontally opposed temporal ports and resulted in significant injury to the carotid arteries, optic apparatus, and temporal lobes in many patients. Current use of multiorport radiotherapy has led to refinement of the technique and improvement in outcome. Conventional fractionated radiotherapy to treat pituitary tumors still carries a risk of delayed optic neuropathy and a 50 to 100% rate of long-term pituitary hormone deficiency.\textsuperscript{17,19} Moreover, conventional fractionated radiotherapy must be administered in 20 to 25 fractions, which is less convenient for the patient, and development of radiation-induced neoplasms such as glioblastoma multiforme or meningioma occurs at a rate of 2.7% by 10 years.\textsuperscript{1}

In the 1960s, Leksell\textsuperscript{14} developed the GK, which consists of a cobalt radiation source. Collimated radiation beams from the original GK and later models are precise enough to focus on the sella turcica and treat pituitary tumors. In fact, one of the earliest applications of the GK was to treat pituitary problems with such procedures as a radiation-induced hypophysectomy.\textsuperscript{13} Advances in computer guidance and neuroimaging of the pituitary lesions and surrounding normal structures have led to substantial improvements in GKS. Despite the widespread use of GKS for the treatment of pituitary adenomas, however, many unanswered questions regarding long-term tumor control, dose, and complications remain.

The present report comprises the largest series of GKS-treated patients with nonfunctioning pituitary adenomas. Of 46 patients with nonfunctioning pituitary adenomas, tumor control was achieved in 93%. Forty-one (89%) of the patients treated had undergone at least one prior form of treatment such as transsphenoidal resection, craniotomy, or radiotherapy. Of the five patients in whom GKS was performed as the primary treatment modality, all tended to be elderly individuals considered ineligible for surgical intervention. Radiosurgery controlled all microadenomas, whereas only 91% of macroadenomas were controlled. Radiosurgery was nearly equally efficacious for pituitary adenomas that exhibited suprasellar extension and those with cavernous sinus invasion.

Other authors have reported similar findings with regard to the efficacy of radiotherapy and radiosurgery for nonfunctioning pituitary adenomas. For instance, Milker-Zabel et al.\textsuperscript{20} reported a tumor control of 97% of their patients (41 of 42 cases) with nonfunctioning adenomas treated with fractionated stereotactically guided radiotherapy. Reporting on 26 patients with nonfunctioning pituitary adenomas, Mokry et al.\textsuperscript{22} achieved a tumor control rate of 96% with GKS. In a series of 23 patients with nonfunctioning adenomas, Izawa et al.\textsuperscript{7} noted a radiosurgery-induced tumor control rate of 95.6%. Near-complete control of tumor growth has been noted in other smaller series of patients with nonfunctioning adenomas.\textsuperscript{5,27}

Pituitary adenomas appear to have varied degrees of radiosensitivity. Nonfunctioning pituitary adenomas seem to require a lower radiation dose than functioning adenomas.\textsuperscript{7,9,16,22,23,27} The lowest effective dose for a nonfunctioning tumor is not known. The lowest effective radiation dose in this series was 10 Gy delivered to the tumor margin; the mean marginal dose was 16 Gy. This is consistent with the doses of 7.6 to 25.4 Gy reported in the literature.\textsuperscript{7,9,15,21–23,27}

We found that five to six isocenters were typically needed to achieve adequate dose planning for a pituitary adenoma. The collimators used in order of decreasing frequency were: 8, 14, 4, and 18 mm. Others have reported using a mean of 2.3 to 6 isocenters per adenoma and the common usage of the 8-mm collimator.\textsuperscript{15,22,24} Stephanian et al.\textsuperscript{28} noted that 4-mm isocenters are theoretically best for limiting the single-fraction dose to the optic apparatus to less than 8 Gy. Isocenters of 8 mm or larger, however, or may be used to treat pituitary adenomas provided the maximum dose does not exceed 50 Gy.\textsuperscript{28}

**Treatment-Related Complications**

The major complication associated with radiosurgery is damage to the optic apparatus. The limited radiosurgery dose to the optic nerves and chiasm is generally recommended to be less than 8 Gy.\textsuperscript{12,29} Damage to the visual system is unlikely when the dose is appropriately limited.\textsuperscript{7} In patients who have undergone surgical reduction of the adenoma, great effort should be made to treat the residual tumor radiosurgically with a clearance of at least 5 mm between the tumor margin and the optic apparatus. Mokry et al.\textsuperscript{22} reported a mean optic nerve dose of 8.1 Gy in patients with nonfunctioning pituitary adenomas, and visual function remained stable in all patients in that group. Similarly in the present series, great effort was made to restrict the radiation dose to the optic apparatus to less than 8 Gy. Collimator channel blocking was also used to shape the radiation field and reduce the dose delivered to the optic apparatus as previously described.\textsuperscript{28}

Despite these efforts, the two patients in whom visual function declined received doses of radiation to the optic apparatus of 8 Gy or less. In these patients tumor growth was demonstrated on follow-up imaging, however, and both underwent repeated transsphenoidal resection. Al-
Radiosurgery for nonfunctioning pituitary adenoma

though one cannot be certain, the visual decline was more likely a result of tumor growth and optic apparatus compression than radiation-induced injury. Delayed radiation-induced injury to the optic nerves could also have contributed to the visual deterioration. Regardless of the efficacy of radiosurgery for most nonfunctioning pituitary adenomas, the tumor progression and visual deterioration observed in 43% of patients in this series emphasize the need for close clinical and radiographic follow-up evaluation.

For those adenomas with cavernous sinus involvement, vascular structures and the third through sixth cranial nerves are generally less susceptible to radiation damage. As such, the limitation of the radiation dose can be somewhat relaxed in laterally reaching adenomas compared with suprasellar ones abutting the optic apparatus. A rare case of cerebral infarction and internal carotid artery occlusion was reported in one patient after undergoing GKS for pituitary adenoma. In the present series, no evidence of a new cranial neuropathy was noted following radiosurgery. Additionally, neither clinical nor radiographic evidence of vascular injury was observed after GKS.

Endocrinopathies can occur after GKS. While planning the dosage, attempts should be made to avoid exposing the pituitary stalk and obvious normal pituitary gland to excess radiation. In the present series, endocrinological deficiencies were present in 30 patients prior to radiosurgery. Many of the patients suffered panhypopituitarism and were receiving suitable hormone replacement therapy. Although none of the endocrinopathies was noted to have worsened after GKS, one patient’s endocrinopathy improved. The underlying mechanism for this improvement is not known.

Two patients whose pituitary adenomas were found to have decreased in size experienced either the onset or worsening of headaches after GKS. Headaches have been known to be associated with pituitary tumors. The exact cause of the headaches in these two patients cannot be known. Nevertheless, the headaches may have been a result of transient swelling prior to tumor shrinkage, as has been observed in cases of vestibular schwannoma treated with radiosurgery.

CONCLUSIONS

Gamma knife surgery appears to be both safe and effective in treating nonfunctioning pituitary adenomas. Long-term tumor control rates of 93% can be achieved in nonfunctioning pituitary adenomas. Radiosurgery is efficacious as an initial treatment modality and a salvage procedure following postresection recurrence. Treatment of patients harboring nonfunctioning pituitary adenomas should be tailored to the patient’s symptoms, overall health, and tumor morphometry. A multidisciplinary team composed of experts in endocrinology, resection, radiosurgery, and radiation oncology should help each patient arrive at a decision regarding the most appropriate treatment plan.

The risks of endocrinopathy, visual dysfunction, or headaches associated with radiosurgery appear to be quite low. Nevertheless, delayed tumor recurrence or growth can arise and underscores the need for meticulous clinical and radiographic follow-up examination of patients. Moreover, the continued follow-up evaluation of patients in this series as well as those at other institutions will help better define the role of radiosurgical treatment for nonfunctioning pituitary adenomas.

References


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